THE DIVISION OF INTRAMURAL RESEARCH

NAEHS COUNCIL REPORT

FEBRUARY 2000

DIR Recruits in Progress

Scientific Director
Dr. J. Carl Barrett, Scientific Director), has accepted an offer to become Director of the Division of Basic Sciences at the National Cancer Institute and will resign as Scientific Director of the NIEHS as of April 1, 2000. Dr. Barrett's energetic, innovative leadership of the Division of Intramural Research during the past five years will be missed by all of the NIEHS. A search for a new Scientific Director is being conducted by the Office of the Director, NIEHS.

Director—Environmental Toxicology Program
Dr. George Lucier, Director, Environmental Toxicology Program and Associate Director, National Toxicology Program (NTP), has announced his intention to retire. He has been a high profile leader of the ETP and the NTP, who has made major contributions as a researcher and in areas of environmental health policy. Dr. Lucier's leadership will be missed by the entire institute. A search will soon begin for his replacement. The Director, ETP, plans and develops programs, establishes priorities and operating budgets, selects staff, oversees and directs subordinate managers, coordinates program activities with other government agencies, and achieves ETP goals and objectives. The ETP has over 200 employees. Efforts are conducted primarily through research and development contracts. A search committee chaired by Dr. Kenneth Korach (Scientific Program Director, Environmental Diseases and Medicine Program, and Chief, Laboratory of Reproductive and Developmental Toxicology) has been formed. The selected candidate will be expected to be appointed to the Senior Biomedical Research Service or the Senior Executive Service.

Deputy Director--Environmental Toxicology Program
A Senior Executive Service position of Deputy Director, Environmental Toxicology Program, is being recruited to assist the Director, ETP, in program planning and development, establishment of priorities and operating budgets, selection of staff, oversight and direction of subordinate managers, coordinating program activities with other government agencies, and achievement of ETP goals and objectives. The ETP has over 200 employees, and efforts are conducted primarily through research and development contracts. The search committee, chaired by Dr. Anne Sassaman (Director, Division of Extramural Research and Training, NIEHS) has selected a candidate and forwarded that recommendation to the NIH.

Chief, Laboratory of Pulmonary Pathobiology
A national search for a new Chief of the Laboratory of Pulmonary Pathobiology (LPP) is taking place. The LPP is engaged in research on the biology of the respiratory tract system at the cellular, biochemical and molecular level to develop a better understanding of pathogenetic mechanisms involved in development of airway diseases. Dr. Perry Blackshear (Clinical Director) is chair of the search committee, which is currently evaluating applications.

Staff Scientist Biostatistician—Toxicology
A tenure-track or tenured Biostatistician is being recruited to assume responsibility for maintaining the statistical integrity of toxicological research carried out at the NIEHS. The work will involve independent statistical research related to models required by new research initiatives and collaboration in the design, analysis, and interpretation of experiments. These activities could include, but are not limited to, analysis of the two-year rodent carcinogenesis bioassay, analysis of shorter term studies with transgenic rodents, development of methods of analysis for short term in vitro assays, and development of methods of analysis for reproductive

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toxicology studies. The search committee is chaired by Dr. Christopher Portier, Chief, Laboratory of Computational Biology and Risk Analysis. The committee has recommended a selection.

Biostatistician—Reproductive Toxicology and Epidemiology
A tenured or tenure-track applied biostatistician with expertise in both reproductive toxicology and reproductive epidemiology is being recruited. The individual selected will provide collaborative support to reproductive toxicologists and reproductive epidemiologists; serve as a bridge between laboratory and human studies of reproduction; and conduct independent research related to the development of new statistical methods for studies designed to identify and characterize effects of environmental toxicants. The search committee is chaired by Dr. Donna Baird (Epidemiology Branch). A short list of candidates to be interviewed has been selected and visits of these candidates are being scheduled.

Staff Scientist—Developmental Toxicology
The Laboratory of Toxicology is seeking a highly motivated, experienced scientist with expertise in the area of developmental toxicology and a strong foundation in molecular and developmental biology. This individual will be expected to integrate the findings from animal studies into improved risk assessments; to conceive, design, and conduct investigations on mechanisms of developmental toxicology; and to publish evaluations and findings in leading biology and toxicology journals. Approximately 75% of the applicant's effort will be devoted to bringing an in-depth knowledge of developmental toxicology to the range of activities carried out by the National Toxicology Program and 25% of the applicant's effort will be devoted to an independent research program that is relevant to the National Toxicology Program. The search committee is chaired by Dr. Robert Chapin (Laboratory of Toxicology). A short list of candidates are currently being interviewed.

Staff Scientist—Report on Carcinogens
The National Toxicology Program is recruiting a Staff Scientist to assist in the preparation of the Biannual Report on Carcinogens. The successful candidate is expected to serve as a expert resource on the toxicology of specified substances, agents, or exposure circumstances under consideration for listing in the Report on Carcinogens. Specific responsibilities will include providing scientific review and coordination for the preparation of background documents; summarizing available information on the toxicology, epidemiology, and human exposure of specified substances; participating in multistep reviews of substances nominated for listing in the Report on Carcinogens; and serving as project officer with oversight responsibility for the contract supporting preparation of the Report on Carcinogens. The search committee is chaired by Dr. Freya Kamel (Epidemiology Branch). A short list of candidates are currently being interviewed.

Staff Scientist--Chief, Veterinary Medicine Section
The Comparative Medicine Branch is seeking a laboratory animal veterinarian with responsibility for the performance of research in the field of laboratory animal medicine to meet the scientific needs of NIEHS. The successful candidate will plan and coordinate independent research studies as well as collaborative studies with NIEHS scientists. Other duties include supervising veterinary medical technicians; assuring veterinary care and preventative health services for a large small animal population (including transgenic and knock-out mice plus rabbit, rat, amphibian and fish species); assuring compliance with federal regulations and policies; consulting with, and providing technical and surgical assistance to, NIEHS researchers;

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reviewing animal study proposals; and developing Standard Operating Procedures. Responsibilities also include development and participation in investigator and technician training programs and training laboratory animal medicine post-doctoral fellows. The search committee was chaired by Dr. John Pritchard (Laboratory of Pharmacology and Chemistry). Dr. Terry Blankenship Paris has accepted the position and will start on March 13, 2000.

Staff Scientist--Veterinary Pathologist

The Laboratory of Environmental Pathology is seeking a highly motivated Toxicologic Pathologist experienced in rodent toxicology and carcinogenicity studies to work within the National Toxicology Program (NTP). The successful candidate will be involved primarily in the management and oversight of the pathology peer review (evaluation), and interpretation and reporting of the data. The candidate will also be expected to identify and pursue special projects that will advance the understanding of various biological endpoints. The search committee, chaired by Dr. Diane Forsythe, Chief, Comparative Medicine Branch, is reviewing applications.

Staff Scientist—Toxicologist

The Toxicology Operations Branch, National Toxicology Program (NTP), is recruiting to fill a non-laboratory position of Toxicologist/Staff Scientist. The successful applicant will serve as a study scientist in the General Toxicology Group and will characterize the biological-toxicological effects from exposure to specifically assigned chemicals and/or agents; plan and provide scientific oversight in the conduct of laboratory studies; evaluate and publish results and serve as a resource of expertise regarding the toxicology of the specified chemicals or groups of chemicals assigned. A search committee chaired by Dr. June Dunnick, Toxicology Operations Branch, has been selected and the position is currently being advertised.

Tenure Track Neuroscientists

The Division of Intramural Research is recruiting for positions that will complement or expand ongoing activities in neuropharmacology, neuroimmunology, signal transduction, synaptic plasticity, reproductive and developmental toxicology and neurotoxicology and invites applications in developmental neurobiology, clinical neuroscience/neuropathology, environmental medicine and neurodegeneration, cellular/molecular neurotoxicology and neuroendocrinology. The search committee is chaired by Dr. Jean Harry, Laboratory of Toxicology. The position is currently being advertised.

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New Appointments in the Division of Intramural Research

Dr. Paul Nettesheim
Dr. Paul Nettesheim has agreed to serve as Acting Scientific Director until a permanent replacement can be identified. Dr. Nettesheim has had a distinguished career as a scientist within the DIR. As Chief of the Laboratory of Pulmonary Pathobiology, he has long served in an important leadership position here and has been responsible for the nurturing and advancement of many scientists at the NIEHS, including Dr. Barrett.

Dr. Richard Paules
Dr. Richard Paules has been appointed to the position of Staff Scientist--Toxicogenomics Facilitator in Molecular Toxicology in the Laboratory of Environmental Carcinogenesis and Mutagenesis (LECM) and the National Toxicology Program (NTP). Dr. Paules is expected to develop leadership for the NIEHS and NTP in molecular toxicology and to facilitate collaborative efforts between NIEHS and other government agencies (such as EPA, FDA, NIOSH), with the academic community, and with the private sector in developing and utilizing the new technologies. He will be expected to devote 50% effort to the NIEHS cDNA microarray facility, 25% to programmatic NTP responsibilities, and 25% to basic research.

Dr. Paules' basic research investigates cell cycle control alterations during carcinogenesis, cell cycle checkpoint signal transduction pathways, oncogene and tumor suppressor signal transduction pathways, and ataxia telangiectasia (AT) gene product function. His research focuses particularly on critical control points in cell cycle transitions. A variety of activated oncogene and tumor suppressor gene products have been shown to interact with cell cycle signal transduction pathways. Although certain environmental agents, including radiation, caffeine, certain toxins, and certain chemicals with tumor promoting properties, have been found to modulate these regulatory pathways, the interaction of cell cycle control mechanisms with most environmental toxins are unknown. These pathways thus hold a potential for being sensitive indicators for induction of proliferative diseases following chemical and/or physical environmental insults. Studies are underway to investigate the molecular mechanisms involved in cell cycle checkpoint responses to exposures to ionizing radiation (IR) and other environmental agents in normal human fibroblasts and in fibroblasts that lack normal function of p53, pRB, or the ataxia telangiectasia (AT) cancer susceptibility gene products. Normal human fibroblasts respond to exposure to IR by rapidly delaying entry into mitosis with an associated strong inhibition of p34cdc2/cyclinB protein kinase activity. AT fibroblasts exposed to IR show little delay of entry into mitosis or inhibition of kinase activity. The rapid G2 checkpoint response to IR does not require p53, pRB, or p21 function. However, lack of p53 results in a progressively increasing proportion of cells losing their G2 checkpoint function that is strongly correlated with the proportion of cells with chromosomal abnormalities. In at least one case, loss of G2 checkpoint function and the appearance of chromosomal abnormalities was accompanied by a reduction in ATM protein levels. Normal human fibroblasts also respond to exposure to IR by delaying the initiation of DNA synthesis with an arrest in G1 that is accompanied by an increase in levels of p21 protein and an inactivation of G1 cyclin/cyclin-dependent kinase (CDK) activity. AT fibroblasts are defective in this induction of p21 and fail to generate a G1 delay following IR exposure. Dr. Paules has recently found that AT cells will arrest in G1 with high levels of p21 under certain circumstances. He is also interested in the role of the ATM gene product in cell cycle checkpoint responses to exposures to environmental carcinogens and particularly the signaling pathways that are generated from broken DNA to the inactivation of cyclin/CDK protein kinase complexes. Recently he found that exposure of normal human

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fibroblasts to reactive oxygen species generated from treatment with t-butyl hydroperoxide results in strong G_1 and G_2 checkpoint responses. In contrast, *ATM*-deficient fibroblast are defective in both G_1 and G_2 checkpoint responses to this oxidative stress and are hypersensitive to the toxic effects of t-butyl hydroperoxide treatment. He has also found that treatment of normal human fibroblasts with either IR or reactive oxygen species results in an activation of the pATM-associated *in vitro* kinase activity, an activity that is lacking in cells lacking pATM. In addition to aiding the understanding of the process of carcinogenesis, these studies hold great potential for providing insight into the mechanism of action of environmental toxins, and particularly those that have been classified as non-genotoxic carcinogens.

Selected Publications:

Paules, R.S., R.W. Tennant, J.C. Barrett, and G.W. Lucier (1999) Bringing genomics into risk analysis: the promises and problems. Inside EPA Risk Policy Report, 6, 30-33.

Ashburner, B.P., R.E. Shackelford, A.S. Baldwin, Jr., and R.S. Paules. 1999. Lack of Involvement of Ataxia Telangiectasia Mutated (ATM) in Regulation of Nuclear Factor-κB (NF-κB) in Human Diploid Fibroblasts. Cancer Res., 59, 5456-5460.

Shackelford, R.E., W.K. Kaufmann, and R.S. Paules. 1999. Cell cycle control, checkpoint mechanisms, and genotoxic stress. Environ. Health Perspect., 107(Suppl. 1), 5-24.

Kaufmann, W.K., J.L. Schwartz, J.C. Hurt, L.L. Byrd, D.A. Galloway, E. Levedakou, and R.S. Paules. (1997) Inactivation of G2 checkpoint function and chromosomal destabilization are linked in human fibroblasts expressing Human Papillomavirus Type 16 E6. Cell Growth Differ., 8, 1105-1114.

Rhodes, N., C.L. Innes, F. Propst, and R.S. Paules. (1997) Serum starved v-mos-transformed cells are unable to appropriately downregulate cyclins and CDKs. Oncogene, 14, 3017-3027.

Afshari, C.A., N. Rhodes, R.S. Paules, and M. Mudryj. (1997) Deregulation of specific E2F complexes by the v-mos oncogene. Oncogene, 14, 3029-3038.

Kaufmann, W.K. and R.S. Paules. (1996) DNA damage and cell cycle checkpoints. The FASEB J., 10, 238-247.

Levedakou, E.N., W.K. Kaufmann, D.A. Alcorta, D.A. Galloway, and R.S. Paules. (1995) p21CIP1 is not required for the early G2 checkpoint response to ionizing irradiation. Cancer Res., 55, 2500-2502.

Paules, R.S., E.N. Levedakou, S.J. Wilson, C.L. Innes, N. Rhodes, T.D. Tlsty, D.A. Galloway, L.A. Donehower, M.A. Tainsky, and W.K. Kaufmann. (1995) Defective G2 checkpoint function in cells from individuals with familial cancer syndromes. Cancer Res., 55, 1763-1773.

Dr. Scott Masten

Dr. Scott Masten was recently recruited for the Staff Scientist in Exposure Assessment position in the Office of the Program Director, Environmental Toxicology Program (ETP). In this position, he coordinates ETP activities in Exposure Assessment and also serves as Head of the Office of Chemical Nomination and Selection. Dr. Masten received his Ph.D. in Pharmacology and Toxicology and was formerly a post-doctoral fellow in the Laboratory of Computational Biology and Risk Analysis at NIEHS. His research background is in mechanistic toxicology and molecular epidemiology.

In a broad sense, these human exposure assessment activities seek to identify research needs and coordinate research efforts for the NIEHS and NTP to assess the magnitude of human health risks posed by environmental and occupational exposures to chemicals and agents. Specific

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priorities include the use of exposure information to establish research priorities for the NTP and other agencies and programs, the use of species comparisons for the evaluation of exposure response relationships, and developing interagency interactions to pursue exposure assessment research priorities. He also collaborates with other NIEHS staff and outside scientists to determine levels of human exposure to known toxic and/or substances through literature reviews, scientific evaluations, and collaborative research projects. Responsibilities in the Office of Chemical Nomination and Selection include coordination of the process by which chemicals are nominated and selected for toxicological evaluation by the National Toxicology Program (NTP). These activities include receiving outside nominations as well as actively identifying substances of potential human health concern that will be the focus of NTP studies. NTP studies are designed to investigate mechanisms of toxicity and carcinogenicity, enhance knowledge of chemical structure/activity relationships, and reduce the uncertainty in risk assessment. An important component of the nomination and selection process is the coordination of public and interagency reviews for NTP nominations to ensure that the NTP evaluations are meeting regulatory and public health needs.

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Awards and Honors in the Division of Intramural Research

Dr. Skip Matthews, Head of the Chemistry Section of the Laboratory of Pharmacology and Chemistry in the Environmental Toxicology Program at the NIEHS, has been named the Society of Toxicology Congressional Fellow for the year 2000. The SOT Congressional Fellowship provides experienced researchers the opportunity to work on scientific issues that are currently being debated in Congress and to contribute scientific and technical expertise to the process of developing public policy. Dr. Matthews will be integrated into the staff of a Congressional committee as a special assistant in which capacity he will serve as a scientific resource, applying his technical knowledge and the scientific method to a variety of public policy concerns. As an SOT Congressional Fellow, Dr. Matthews will interact with members of Congress, other staffers, lobbyists, regulatory agency representatives, and citizens. Among his duties will are included writing background papers for members of Congress or staffers, critiquing reports submitted by federal agencies or by lobbying groups, and making presentations to the staffs of other committees.

Dr. Trevor Archer (Laboratory of Reproductive and Developmental Toxicology) chaired a session at the West Coast Chromatin and Chromosomes Meeting, Dec 16-19 at Pacific Grove CA;

Dr. J. Carl Barrett (Scientific Director and Chief, Laboratory of Molecular Carcinogenesis) was an invited speaker for the Princess Takamatsu Cancer Research Fund Symposium on "New Frontiers in Mechanistic Cancer Research in Animal Models", Tokyo , Nov. 16-18 and the Samuel Kuna Distinguished Lecturer, Rutgers, The State University of New Jersey, November 1999

Dr. Gary Boorman (National Toxicology Program) assumed the presidency of the American College of Veterinary Pathologists (ACVP) on January 1, 2000.

Dr. Diane Forsythe was installed as a member of the Board of Directors of the American College of Laboratory Animal Medicine (ACLAM) and was given an NIH Merit Award for Y2K Preparedness of the NIEHS Animal Care and Use Program

Dr. Dori Germolec (Laboratory of Toxicology) was elected Vice-President of the Immunotoxicology Specialty Section of the Society of Toxicology, and will be President of the Specialty Section starting in May, 2000.

Ms. Tara Lovekamp, a graduate student in NCSU Toxicology Program and a pre-doctoral IRTA in the Laboratory of Women's Health, has received a Graduate Student Travel Award for the 2000 Annual Meeting of the SOT. The award was based on her abstract titled "Mono-(2-Ethylhexyl) Phthalate Suppresses Estradiol By Decreasing Aromatase Mrna Expression Level As Shown By Real Time RT-PCR.

Dr. Dale Sandler (Deputy Chief, Epidemiology Branch) started her term as President of the American College of Epidemiology in October 1999.

Dr. Raymond Tennant (Chief, Laboratory of Experimental Carcinogenesis and Mutagenesis) was Chairperson and an invited speaker for the Princess Takamatsu Cancer Research Fund Symposium on "New Frontiers in Mechanistic Cancer Research in Animal Models", Tokyo Nov. 16-18.

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Training and Mentoring Activities

The NIEHS Trainees Assembly (NTA) has selected new leadership for the upcoming year. Dr. Deborah Swope (Laboratory of Reproductive and Developmental Toxicology) has been selected Chair of the NTA. Dr. Brian Vande Berg (Laboratory of Structural Biology) will serve as the NTA Assistant Chair. Both Debbie and Brian will also serve as the NIH FELCOM representatives. Ms. Bonnie Deroo, a graduate student and a member of the NTA steering committee, will serve as the NIEHS representative on the Pre-IRTA committee.

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The Division of Intramural Research Retreat

The second annual Division of Intramural Research Retreat, organized by Dr. Michael Hogan, was held at the Pine Needles Lodge in Southern Pines, NC on January 5-7, 2000. The program began with reports by the Dr. J. Carl Barrett (Scientific Director) and Dr. Anne Sassaman (Director, Division of Extramural Research and Training) and a presentation by Dr. George Lucier (Director, Environmental Toxicology Program) titled "Environmental Toxicology—past, Present, and Future." The following day, scientific presentations were made by the "New Faces in the DIR": Dr. Fed Miller (a candidate for a clinical research position in the Laboratory of Women's Health Research), Dr. Glinda Cooper (Epidemiology Branch), Dr. Freja Kamel (Environmental Toxicology Program and the Epidemiology Branch), Dr. Bennett van Houten (Laboratory of Molecular Genetics and the Division of Extramural Research and Training), and Dr. Richard Sharp (Office of the Scientific Director). In the afternoon, presentations were given describing New Technologies at the NIEHS by Drs. Richard Paules (cDNA Microarray), Cynthia Afshari (cDNA Microarray), Nigel Walker (quantitative PCR), Alex Merrick (proteomics), Kenneth Tomer (proteomics), Christoph Borchers (proteomics), Ms Julie Foley (laser capture microdissection), Drs. Vladimir Larionov (TAR cloning), Rachel Beinstock (molecular modeling), David Miller (confocal microscopy), and Mr. Bill Quattlebaum (computing needs). The last session of the retreat consisted of breakout groups charged with considering such issues as the balance between permanent staff and post-doctoral fellows, training programs, the portrayal of the NIEHS to the public, new directions for the DIR, and adjunct appointments. The retreat closed with a discussion of the results of the breakout groups and a presentation by the NIEHS Trainees Assembly. In all, there were approximately 100 participants.

Technology Transfer Activity for FY 1999

Material Transfer Agreements

NIEHS scientists participated in 180 Material Transfer Agreements (MTAs) in FY 1999. Of these, 76% were completed with academic institutions; the remaining 24% were with pharmaceutical/biotechnology commercial organizations. The majority of NIEHS MTA scientific collaboration (78%) took place within the United States, and the remainder with foreign institutions throughout the world, mainly in Australia, Europe and Japan.

Employee Invention Reports

Thirteen Employee Invention Reports (EIRs) or EIR actions were reviewed and approved by Dr. John Penta, the NIEHS Technology Development Coordinator. Following review and recommendation by the NIEHS Technology Evaluation Advisory Committee, chaired by Dr. David Armstrong (Laboratory of Signal Transduction), and/or the NIEHS Scientific Director, the following approved EIRs were forwarded to Bethesda for patent action by the NIH Office of Technology Transfer in FY 1999:

Name of Invention	NIEHS Inventor	Laboratory/Branch
Fluorescent magnesium indicators	Dr. Robert London	Laboratory of Structural Biology
Novel gene family for DIPPS	Dr. Stephen Shears	Laboratory of Signal Transduction
Cloning expression and diagnosis of human cytochrome P450 2C19	Dr. Joyce Goldstein	Laboratory of Pharmacology and Chemistry
TTP inhibitors as agents to stabilize GM-CSF	Dr. Ester Carballo Dr. Perry Blackshear	Laboratory of Signal Transduction
Method for modulating processes mediated by farnesoid activated receptors	Dr. Cary Weinberger	Laboratory of Reproductive and Developmental Toxicology
Targeting of human genes in chicken B cell hybrids containing human chromosomes	Dr. Koi	Laboratory of Molecular Carcinogenesis
Pharmaceutical compositions comprising clozapine and a radical scavenger	Dr. Ronald Mason	Laboratory of Pharmacology and Chemistry

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A genetic system in yeast for functional identification of human p53 mutations	Dr. Michael Resnick	Laboratory of Molecular Genetics
A genetic system in yeast for turning p53 mutant protein into a toxin	Dr. Michael Resnick	Laboratory of Molecular Genetics
Compositions comprising vitamin F	Dr. Cary Weinberger	Laboratory of Reproductive and Developmental Toxicology
Antiinflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids	Dr. Darryl Zeldin	Laboratory of Pulmonary Pathology
Structured combinatorial queries for characterizing and comparing biological sequences	Dr. Ken Tomer	Laboratory of Structural Biology
Soluble epoxide hydrolase inhibitors for managing systemic hypertension	Dr. Darryl Zeldin	Laboratory of Pulmonary Pathology

Thirteen CRADAs or M-CRADAs were initiated or activated with commercial organizations on behalf of NIEHS scientists:

Genetics Institute (for Dr. Richard DiAugustine, Laboratory of Molecular Carcinogenesis).
Glaxo Wellcome (for Dr. Carl Barrett, Laboratory of Molecular Carcinogenesis).
Monsanto (for Dr. John Hong, Laboratory of Pharmacology and Chemistry).
Novartis (for Dr. Carl Barrett, Laboratory of Molecular Carcinogenesis).
Novartis (for Dr. Anton Jetten, Laboratory of Pulmonary Pathology).
Novartis (for Dr. David Armstrong, Laboratory of Signal Transduction).
Paradigm Genetics (for Dr. Cynthia Afshari, Laboratory of Molecular Carcinogenesis).
Inologic, Inc. (for Dr. Stephen Shears, Laboratory of Signal Transduction).
Geron Corp. (for Dr. Carl Barrett, Laboratory of Molecular Carcinogenesis).
Boehringer-Ingleheim (for Dr. Ray Tennant, Laboratory of Experimental Carcinogenesis and Metastasis).
Gilead Sciences (for Dr. John Pritchard, Laboratory of Pharmacology and Chemistry).
AstraZeneca (for Dr. Perry Blackshear, Laboratory of Signal Transduction).
Boehringer-Ingleheim (for Dr. Carl Barrett, Laboratory of Molecular Carcinogenesis).

Highlights from the National Toxicology Program

- The new NTP Center of Phototoxicity houses the jointly operated and recently completed FDA-NIEHS Phototoxicity Research and Testing Laboratory. The Center is located at the FDA's National Center for Toxicological Research (NCTR) in Jefferson, Arkansas. Input into the design of the facility was obtained from experts in photobiology and phototoxicology. The Toxicology Study Selection and Review Committee, which is composed of scientists from FDA, NTP, NIEHS, and others with appropriate expertise, will review the design of experimental protocols and evaluate the progress of research studies. The laboratory is designed for testing the effects of drugs, chemicals used in cosmetic preparations, and/or other agents on UV radiation or simulated solar light-induced toxicity and cancer. This NTP Center will have a significant impact on the quality of public health through the generation of scientific data that can facilitate accurate and mechanistically based determinations of human cancer risk from combinations of drugs or compounds with sunlight.

- The National Toxicology Program established the Center for the Evaluation of Risks to Human Reproduction (CERHR) to provide scientifically based assessments of the evidence for reproductive and developmental toxicity of man-made or naturally occurring chemicals or chemical mixtures. The first evaluation by the Center is a review of phthalates. Phthalates were chosen based on their high production volume, extent of human exposures, use in children's products, and/or published evidence of reproductive or development toxicity. An expert panel was established for the evaluation of seven phthalate esters (butyl benzyl phthalate, di(2-ethylhexyl) phthalate, di-isodecyl phthalate, di-isononyl phthalate: DINP, di-n-butyl phthalate, di-n-hexyl phthalate, and di-n-octyl phthalate) and has met twice, August 17-19 and December 15-17, 1999. To date, a consensus summary statement about the developmental and reproductive toxicity of DINP was developed and discussed by the Panel and will soon be available on the CERHR website (http://cerhr.niehs.nih.gov).

- NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM):
  - ICCVAM, a standing committee composed of representatives from 14 Federal regulatory and research agencies and programs, functions to facilitate cross-agency communication and coordination on issues relating to validation, acceptance, and national/international harmonization of toxicological test methods. An independent peer review panel coordinated by ICCVAM and NICEATM concluded that the murine Local Lymph Node Assay (LLNL) is an acceptable alternative test method to the traditional guinea-pig test for identifying whether or not chemicals may cause allergic contact dermatitis in workers and consumers. *This is the first alternative test method to be reviewed using the ICCVAM process.* The panel's conclusions were forwarded to the various ICCVAM agencies with a request for response and comments on implementation of LLNA. ICCVAM agencies have responded in writing or at a public meeting, October 14, 1999; agency response has been overwhelmingly favorable. The Consumer Product Safety Commission, the Environmental Protection Agency, the Occupational Safety and Health Administration and the Food and Drug Administration concurred with the expert panel

and recently announced that, in most instances, they will accept results from LLNA to assess the allergic contact dermatitis potential of chemicals and will change their regulations accordingly.

- Before a new or revised test method is used to generate information to support regulatory decisions, it must be (a) validated to determine its reliability and relevance for this proposed use and (b) determined to be acceptable by one or regulatory agencies to fill a specific need. ICCVAM has updated its guidance document, *Evaluation of the Validation Status of Toxicological Methods: General Guidelines for Submissions to the Interagency Coordinating Committee on the Validation of Alternative Test Methods,* based upon experience gained with the first two test methods reviewed by ICCVAM in 1998-99. This document provides guidance to test method developers about the information needed by ICCVAM to evaluate the validation status of new or revised test methods at any stage of development and after the completion of validation studies. ICCVAM has solicited public comments on the guidance document and may consider further revisions.
- The next meeting of the NTP Advisory Committee on Alternative Toxicological Methods (ACATM) for NICEATM is scheduled for March 7-8, 2000 at the NIEHS. Topics on the agenda include possible new technologies for toxicological assessments, an update about activities of the Center and IVVCAM, an update on regulatory acceptance of ICCVAM recommended test methods, and the guidance document for submissions of proposed alternative test methods to ICCVAM. ACATM is composed of representatives from academia, industry, public interest organizations, other State and Federal agencies, and the international community. The Committee functions to provide advice on the activities and priorities of the NICEATM and ICCVAM and on ways to foster partnership activities and productive interactions among all stakeholders.
- ICCVAM and NICEATM are planning an Expert Panel Meeting, May 16-18, 2000, to assess the current validation status of the Frog Embryo Teratogenesis Assay - Xenopus (FETAX), a method proposed for assessing the developmental toxicity potential of chemicals. NICEATM is preparing a background document summarizing the initial studies and the performance characteristics of FETAX and soliciting public input on FETAX. The expert panel will evaluate the conclusions presented in the background document, the validation status of FETAX, potential uses of FETAX, and whether additional studies are needed.

- Report on Carcinogens (RoC):
  - The Congress mandated that the RoC be published biennially for the purpose of providing to the public a list of substances that may pose a potential hazard for human health. The NTP prepares the RoC for the U.S. Department of Health and Human Services (DHHS). The 8th RoC was published in 1998 and a lengthy preparation and review process is nearing completion for the 9th Report. The Report discusses individual substances, mixtures of chemicals, or exposure circumstances associated with technological process which are *known to be human carcinogens,* or *reasonably anticipated to be human carcinogens;* it also contains information received from other Federal agencies relating to estimated exposures and exposure standards or guidelines. The nominations under review for listing and delisting in the 9th RoC is listed below.

Under review for listing in the 9th RoC (CAS No.)	Under review for delisting in the 9th RoC (CAS No.)
Alcoholic Beverage Consumption Boot and Shoe Manufacture and Repair 1,3-Butadiene (106-99-0) Cadmium and Cadmium Compounds (7440-43-9) Chloroprene (126-99-8) Diesel Exhaust Particulates Dyes Metabolized to Benzidine (Benzidine Dyes as a class) Environmental Tobacco Smoke Ethylene Oxide (75-21-8) Isoprene (78-79-5) Methyl-t-Butyl Ether (1634-04-4) Nickel Compounds Phenolphthalein (77-09-8) Silica, Crystalline (Respirable Size) (7631-86-9) Smokeless Tobacco Strong Inorganic Acid Mists containing Sulfuric Acid Tamoxifen (10540-29-1) 2,3,7,8- Tetrachlorodibenzo-p-dioxin (TCDD) (1746-01-6) Tetrafluoroethylene (116-14-3) Tobacco Smoking Trichloroethylene (79-01-6) Solar Radiation and Exposure to Sunlamps and Sunbeds	Ethyl Acrylate (140-88-5) Saccharin (218-44-9)

- The 9th RoC generated significant comment on potential listings/delistings as well as on the review process and the evaluation criteria. To provide an opportunity for dialogue and a chance for all interested persons to provide input, the NTP held a public meeting October 21-22, 1999 in Rockville, MD. Dr. Bernard Goldstein, Director of the Environmental and Occupational Health Sciences Institute of Rutgers and the University of Medicine and Dentistry of New Jersey chaired the meeting, and it was well attended with 79 registered attendees and 41 speakers. The participants represented a broad group of stakeholders. Also present were Dr. Kenneth Olden, senior NTP staff, and representatives from the NTP Board of Scientific Counselors and each of the review groups involved with the Report's preparation. Views on some issues (e.g. the quality of the background documents on nominations and the level of involvement of industry scientists in the review process) were polarized. The NTP has reviewed all comments. Changes in the process (e.g., earlier public release of the RoC background documents; holding NTP Board of Scientific Counselors RoC Subcommittee meetings in the Washington, DC area; extending the time for public comment at the Subcommittee meetings) are being considered that will be responsive and will result in improvements.
- The review of nominations for listing/delisting in the RoC is a multi-level process with multiple opportunities for public input. Peer review of nominations by the NTP Board of Scientific Counselors RoC Subcommittee is one level of that review. The Subcommittee's evaluation of the first group of nominations being considered for inclusion in the 10th RoC was conducted January 20-21, 2000 in Alexandria, Virginia. This group includes 2,3-dibromo-1-propanol, 2,2-bis-(bromomethyl)-1,3-propanediol, beryllium and beryllium compounds, dyes metabolized to 3,3'-dimethoxybenzidine (dimethoxybenzidine dyes as a class), dyes metabolized to 3,3'-dimethylbenzidine

(dimethylbenzidine dyes as a class), 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), Styrene-7,8-oxide, vinyl bromide, and vinyl flouride.

- The next meeting of the NTP Board of Scientific Counselors is scheduled for May 24, 2000. The Board is composed of scientists from the public and private sectors and provides scientific oversight to the NTP. One item for the agenda will be an update on the NTP Center for the Evaluation of Risks to Human Reproduction.

- The next meeting of the NTP Board of Scientific Counselors Technical Reports Subcommittee is scheduled for May 18, 2000. This is subcommittee is the part of the NTP Board of Scientific Counselors that evaluates the results from the studies in an open, peer-review meeting. Seven candidate reports are scheduled to be considered at the next meeting: sodium nitrate, methacrylonitrile, *p*-nitrotoluene, indium phosphide, naphthalene, *p-p"*-dichlorodiphenylsulfone, and chloral hydrate. The technical report on naphthalene will be number 500 in the NTP series. The NTP conducts research studies that are designed to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the basis of human exposure, level of production, and chemical structure.

- The NTP is participating in an industry/government consortium to evaluate a number of alternative assays designed to augment or replace the two-year rodent bioassay. The effort, which is coordinated by the International Life Sciences Institute/Health and Environmental Sciences Institute (ILSI/HESI), is comprised of approximately 25 pharmaceutical companies and several government agencies. A set of about a dozen chemicals is being evaluated in five short-term model systems including three genetically altered mouse models, the newborn mouse assay, and the Syrian hamster embryo cell transformation assay. The NTP is testing six chemicals in the Tg.AC model by two routes of administration. An ILSI/HESI organized meeting is scheduled for November 2000 in the Washington, DC area to discuss and evaluate the effort's findings. The results will contribute to an NTP evaluation of genetically engineered mouse models by the Interagency Coordinating Committee for Validation of Alternative Methods that is scheduled for 2001.

- NTP Chemical Nomination and Selection
  - The NTP openly solicits nominations of chemicals and substances for study and receives nominations from a variety of groups including Federal agencies, public, industry, and labor unions. The NTP also welcomes public comments on nominations and information from toxicology and carcinogenesis studies, as well as supplementary data on current production levels, human exposure, use patterns, or environmental occurrence. Nominations for NTP studies undergo several levels of review before toxicological studies are designed and implemented. The following nominated chemicals and substances completed the review process in 1999 and attention is being given for their study by the NTP: aloe vera gel, ammonium molybdate, 5,6-benzoflavone, 1,3-dichloro-2-butene, ginseng and ginsenosides, indole-3-carbinol, Kkava kava extract, milk thistle extract, and 3-picoline.

· The Interagency Committee for Chemical Evaluation and Coordination (ICCEC) serves as the first interagency level of review for NTP nominations. Recommendations by the ICCEC are published in the Federal Register and on the NTP website (http://ntp-server.niehs.nih.gov/NomPage/noms.html) and public input is solicited. The NTP Board of Scientific Counselors and the NTP Executive Committee conduct subsequent reviews of the nominations and consider any public comments received in their deliberations. The ICCEC evaluated the following chemicals at its December 1999 meeting.

Chemicals and substances recommended for testing (CAS No.)	Chemicals and substances for which no testing is recommended (CAS No.)	Chemicals and substances deferred for additional information (CAS No.)
1-Bromopropane (106-94-5) and 2-Bromopropane (75-26-3)	Cafestol (469-83-0) and Kahweol (6894-43-5)	Ethylenebis(tetrabromo-phthalimide) (32588-76-4)
Chitosan (9012-76-4)	Plumbagin (481-42-5)	Terpinolene (586-62-9)
DNA-based products		Tetrabromophthalic anhydride (632-79-1)
Juglone (481-39-0)		Texanol benzyl phthalate (16883-83-3) or (32333-99-6)
Potassium ferricyanide (13736-66-2)		
Radio frequency radiation emissions of wireless communication devices		

- Human Exposure Assessment

1. A key area of current focus is human exposure assessment, as knowledge on human exposures to agents of potential public health concern will aid in selecting agents for priority study, in designing animal bioassays, and in preparing toxicological evaluations and reports. To meet these needs, the NTP is leading a new inter-agency initiative on Human Exposure Assessment in collaboration with NCEH/CDC, NIOSH/CDC, EPA, and others that will strive to provide such information. Some early efforts being undertaken in moving forward with this new initiative include the Human Exposure and Environmental Disease Workshop (see below) and a collaborative project between NIEHS and NCEH to analyze a variety of endocrine disrupting chemicals such as phytoestrogens and phthalate esters in human biological samples.
2. The NTP co-sponsored a workshop, *The Role of Human Exposure Assessment in the Prevention of Environmental Disease*, on September 22-24, 1999 in Rockville, Maryland. The meeting was well attended with 350 registrants from government, academia, industry, and labor and community groups. The Workshop's goals were to describe current opportunities and challenges in exposure assessment research, to provide usable information on disease-specific chemical exposures that will allow integration of epidemiological and toxicology studies, and to highlight approaches for further research and effective prevention and intervention strategies. The meeting's format included plenary overview lectures as well as breakout sessions. A draft summary report from the workshop is provided in your information for this meeting.

- The NTP is co-sponsoring an international conference, *The Efficacy and Safety of Medicinal Herbs*, March 2-3, 2000 at The Friday Center, Chapel Hill, North Carolina. The objectives of the conference are to present up-to-date evidence on effects of some of the frequently used

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herbal and botanical products, to evaluate the research studies testing these products, and to address research challenges and the application of new techniques for studying health effects of these products. Questions about registration can be addressed to the Office of Continuing Education, the University of North Carolina at Chapel Hill (t: 919-966-4032, f: 919-966-5692, email: oce@unc.edu).

- The NTP continues to work toward increasing public outreach about its programs and activities. The NTP recently participated with an exhibit at the 137th Annual American Public Health Association Meeting and Exposition in Chicago, Illinois. This meeting attracted approximately 13,000 public health professionals interested in public health and public health policy.